ΕΠΙΜΟΝΗ ΣΥΜΠΤΩΜΑΤΙΚΗ ΣΑΡΚΟΕΙΔΩΣΗ:
ΠΕΡΑ ΑΠΟ ΤΑ ΚΟΡΤΙΚΟΣΤΕΡΟΕΙΔΗ

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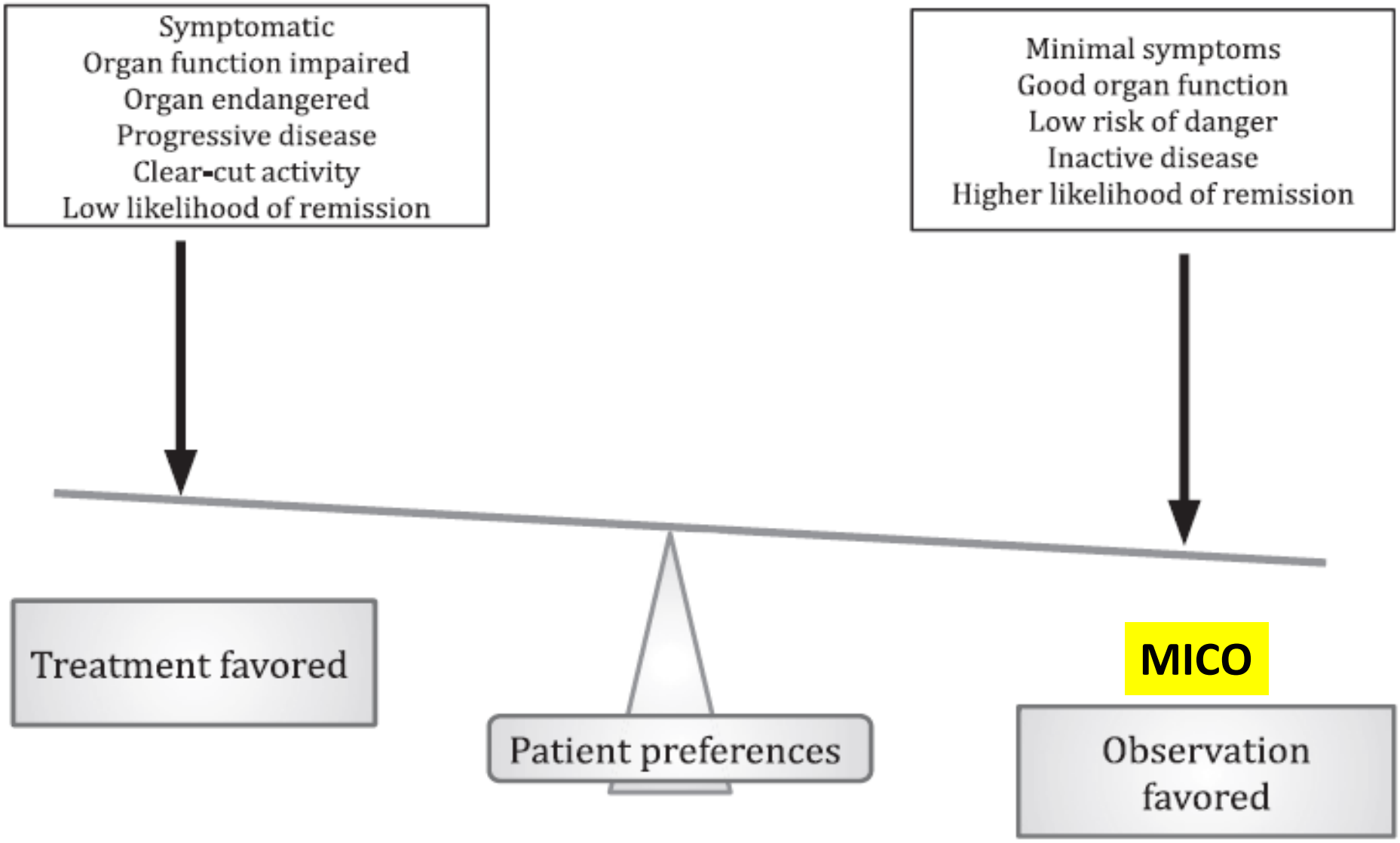
Conflicts of Interest

I declare

NO conflicts of interest

Major factors influencing decision to start immunosuppressive therapy



Chronic SARCOIDOSIS

Taper glucocorticoids to prednisone <10 mg/day or equivalent

Yes:

Continue glucocorticoids alone

Not able to taper

Rule out other causes of symptoms *

Cytotoxic agents

Methotrexate: Level 1A

Azathioprine Level 1C

Leflunomide Level 1C

* Pulmonary hypertension, CHF, muscle weakness, fatigue, infection

	Level of evidence in sarcoidosis	Most common toxic effects (>1%)	Rare but important toxic effects
Methotrexate	Double-blind placebo-controlled trials, prospective case series, case reports	Nausea, mouth ulcers, leucopenia, hepatotoxicity, nausea, infections	Pneumonitis, teratogenic
Azathioprine	Prospective case series, case reports	Leucopenia, nausea, infections	Severe leucopenia, heptatoxic effects, pancreatitis, skin cancer
Leflunomide	Double-blind placebo-controlled trials, prospective case series, case reports	Leucopenia, hepatotoxic effects, infections, alopecia	Pneumonitis, teratogenic, peripheral neuropathy, hypertension
Mycophenolate mofetil	Case series	Nausea, diarrhoea, infections	Skin cancer

Table 2: Antimetabolite therapy

Treat with Methotrexate

Dose 5-15/wk. Level 1A
Folic acid 1 mg/d. Level 1B

Stop MTX Every 2 years

No Further Symptoms

Recurrence of Symptoms

20%

Observe

Restart MTX

Improvement

No Improvement

75%

Liver Biopsy

Try Another Drug

5%

No MTX Toxicity

MTX Toxicity

4%

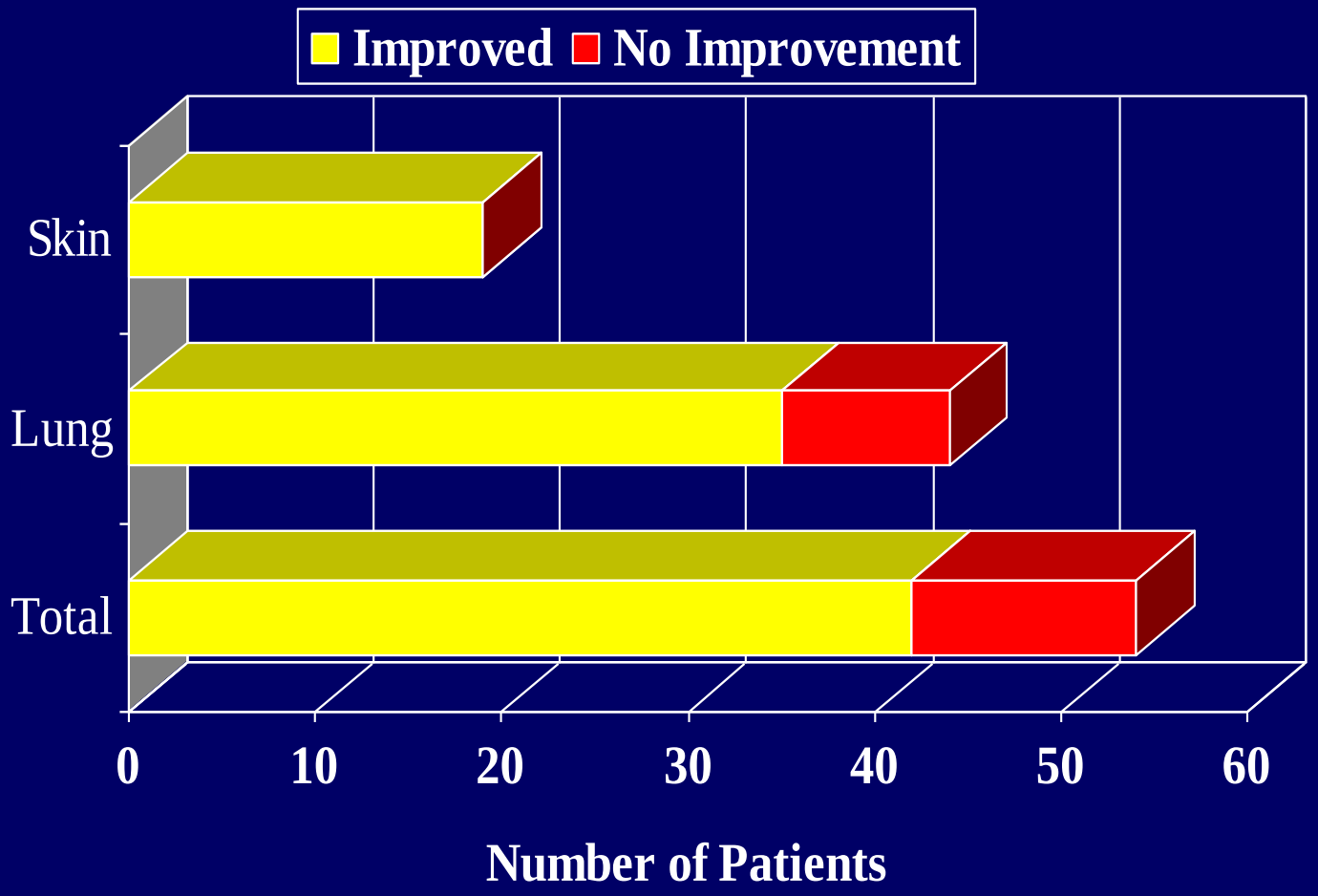
Continue MTX

Try Another Drug

Baughman and Lower. Thorax 1999; 54: 742-746

Treatment with Methotrexate for >2 Years:

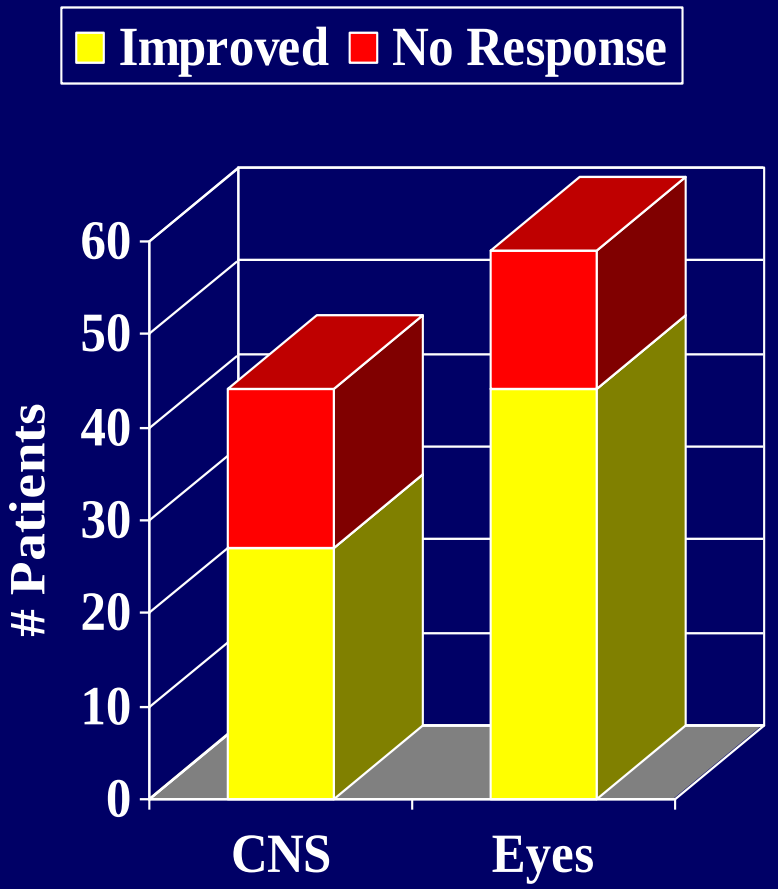
Response to Methotrexate



Lower, Baughman. Arch Intern Med 1995; 155: 846-851

Effectiveness of Methotrexate for Specific Organ Involvement

- **Neurologic disease**
  - Non responders to methotrexate usually treated with cyclophosphamide
- **Eye disease**
  - Non responders to methotrexate usually responded to combination cytotoxic drugs



Lower et al Arch Intern Med 1997
Baughman et al Sarcoidosis

Posterior Trunk Lesions Treated with Methotrexate

BEFORE

AFTER

Effectiveness of Azathioprine

- **Found useful by some authors**
  - *Pacheo et al Sarcoidosis 1985; 2: 107-113*
  - *Muller-Quernheim, et al. Eur Respir J 1999; 14:1117-1122.*
- **Limited utility in patients with chronic lung disease**
  - **Patients with limited response to corticosteroids**
  - **Only 2 of 10 patients with response**
  - *Lewis et al Sarcoidosis 1999; 16: 87-92*
- **Dose 50-200 mg/d. Level 1B**

Leflunomide (Arava)

- Is an immunomodulatory drug
- Similar to methotrexate
- Less gastrointestinal toxicity
- Has been used in combination with methotrexate for rheumatoid arthritis
  - *Kremer JM, et al. Ann Intern Med 2002;137:726-733.*
- Dose 10-20 mg/d po. Level 1B.

Baughman RP, Lower EE Sarcoidosis 2004; 21:43-48

LEFLUNOMIDE FOR SARCOIDOSIS

Evaluation	Total	Eye
Total Number	32	28
Complete Response	16	15
Partial Response	9	8
Complete + Partial Response	25 (78%)	23 (82%)
No Response	4	2
Toxicity	3	3

* Number (percent responders)

Baughman and Lower *Sarcoidosis* 2004; 21:43-48

	Leflunomide alone (n=32)	Leflunomide plus methotrexate (n=33)
Complete response*	12 (38%)	22 (67%)
Partial response†	14 (44%)	6 (18%)
No response‡ or toxic effects	6 (18%)	5 (15%)

Data are n (%) and are from a combination of two case series of sarcoidosis patients.[20,21] *>90% improvement in target organ. †50–89% improvement in target organ. ‡<50% improvement in target organ. An improvement is described as 5–10% improvement in forced vital capacity for lung disease and greater than 50% reduction in lesion for a specific organ, for example a skin lesion or brain mass.

Table 1: Response or toxic effects to leflunomide in patients with chronic sarcoidosis

Leflunomide for Sarcoidosis: 6-9 months of therapy

Cleveland Clinic Experience

	Leflunomide Alone	Leflunomide plus Methotrexate
Total Number patients	19	18
Complete response (>90%)	6 (32%)	13 (72%)
Partial response (50-89%)	9 (47%)	3 (17%)
No response (<50%)	4 (21%)	1 (6%)
Unable to assess	0	1 (6%)

Sahoo DH, et al. Eur Respir J 2011; 38:1145-1150.

Biological agents to block TNF

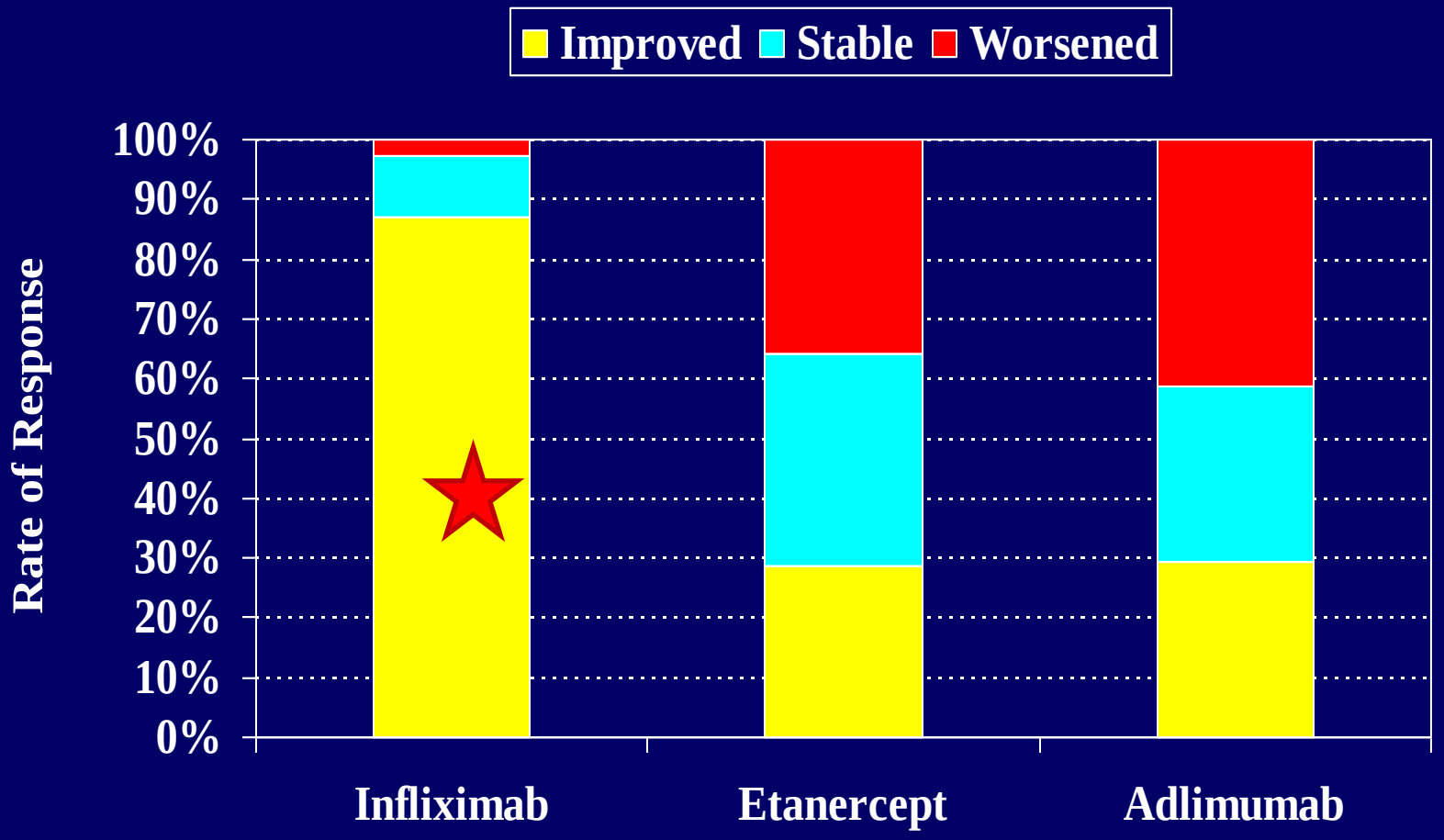
Drug	Mechanism of Action	Administration	Effective in Rheumatoid Arthritis	Effective in Crohn's disease
Etanercept ENBREL	TNF receptor antagonist	Sub cutaneous	Yes	No
Infliximab REMICADE	Chimeric monoclonal antibody	Intra venous	Yes	Yes
Adalimumab HUMIRA	Humanized monoclonal antibody	Sub cutaneous	Yes	Yes *
Golimumab SIMPONI	Humanized monoclonal antibody	Sub cutaneous	Yes	Yes

* In higher doses

Comparison of anti-TNF Agents for Sarcoidosis

- Retrospective study at UC and MUSC
- All patients were treated for at least one month of therapy
- Treatment with either
  - Etanercept
    - 25 mg sq two times a week
  - Infliximab
    - 5 mg/kg week 0, 2, and 6
    - Then every 4-6 weeks
  - Adalimumab
    - 40 mg sq q 1-2 weeks

Response Rate to anti-TNF Therapy



Significant difference in response between groups,
Chi square =36.491 p<0.0001.

Main indications for the use of biological TNFα inhibitors in sarcoidosis

- Unsuccessful treatment with prednisolone and antimetabolites (such as methotrexate)
- Chronic pulmonary disease with decreased forced vital capacity, forced expiratory volume in 1 s, or diffusing capacity of the lung for carbon monoxide, and worsening of chest imaging or positive ^{18}F-fluorodeoxyglucose-PET of the lung
- Debilitation by lupus pernio
- Neurosarcoidosis in persistent disease activity
- Cardiac sarcoidosis in persistent disease activity

Who to treat with anti-TNF therapy

- Improved response if:
  - FVC<70%
  - Dyspnea ≥ 1
  - Disease > 2 years
  - Significant extrapulmonary disease
    - Lupus pernio
    - CNS

- Possible predictors of response
  - Elevated CRP
  - TNF -308 polymorphism

Baughman RP et al. Sarcoidosis 2008; 25: 76-92.

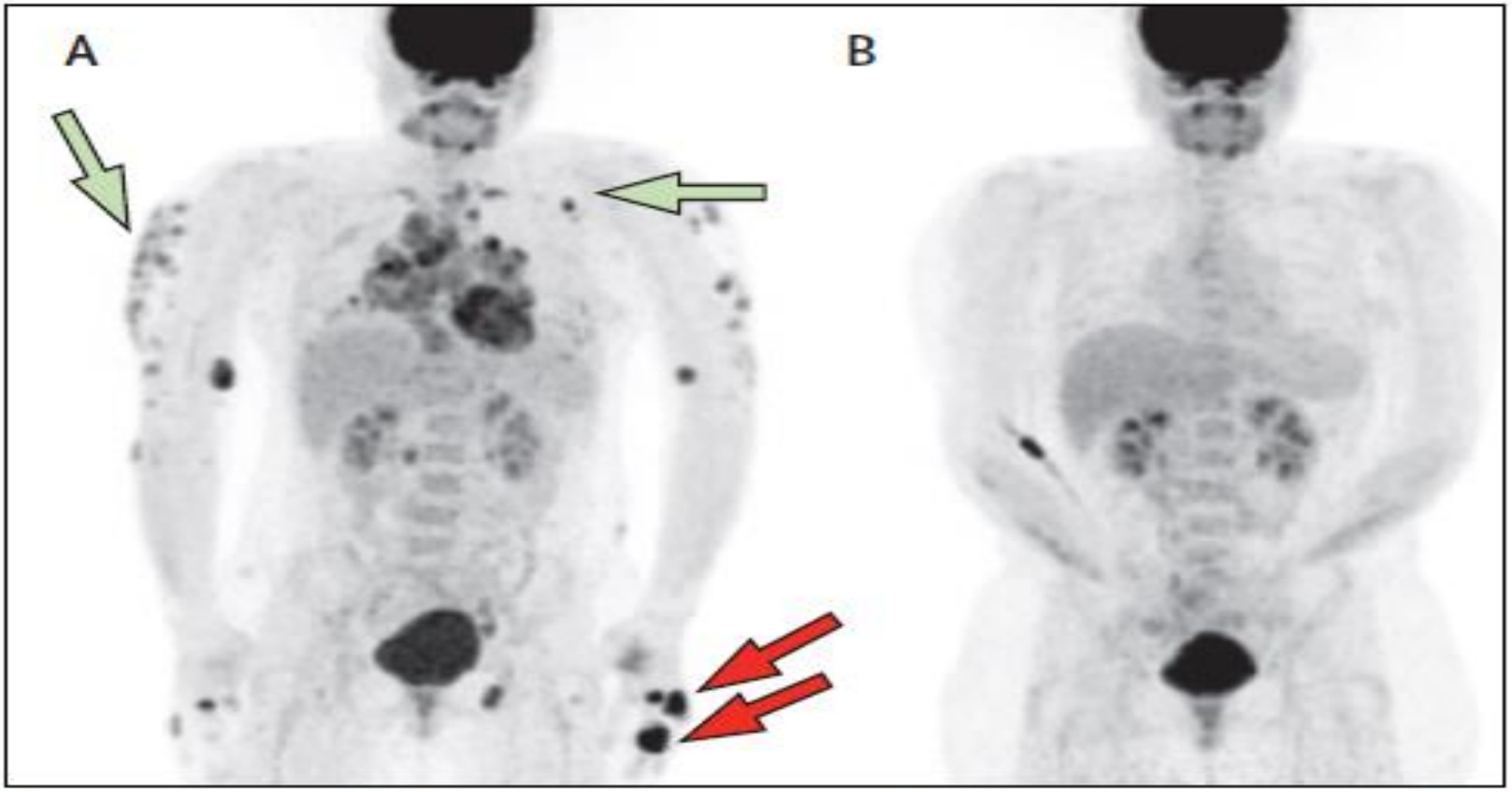


Figure 2: **PET scan of a patient with sarcoidosis before and after 6 months of infliximab treatment**

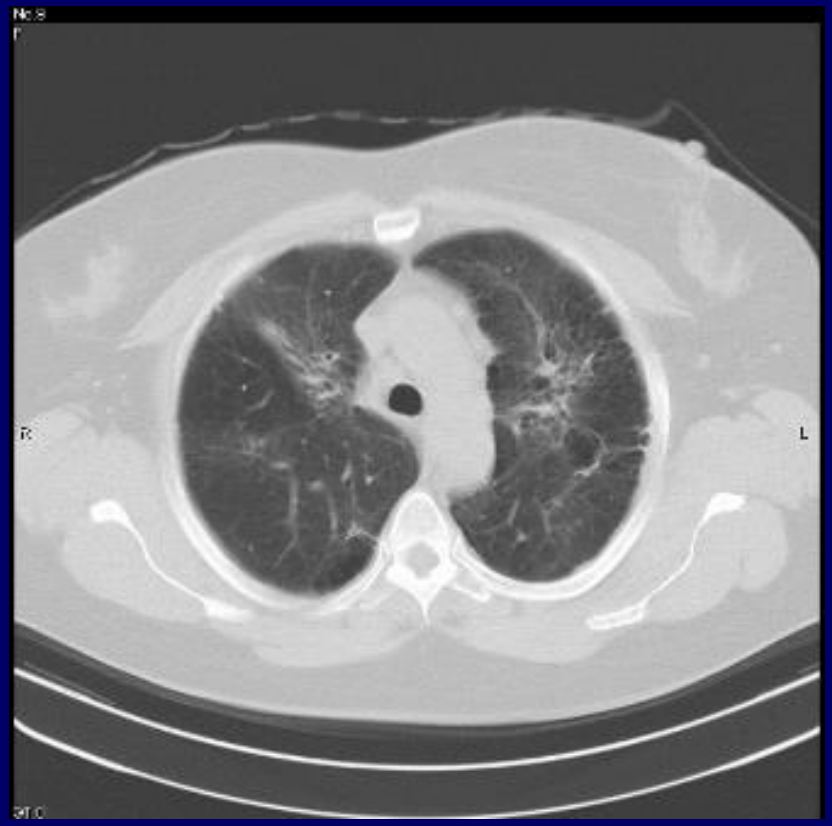
(A) Patient with sarcoidosis showing pulmonary, skin, and lymph-node involvement, arthritis of metacarpophalangeal joints, and osseous involvement of a phalanx, as indicated by increased ^{18}F-fluorodeoxyglucose uptake (green arrows=skin and lymph nodes, red arrows=metacarpophalangeal joints of left hand). (B) The repeated PET scan after 6 months of infliximab therapy. No abnormal uptake can be seen in the skin, lymph nodes, lungs, joints, or skeleton.

Effect of Infliximab on CXR

Before Infliximab

After four cycles of Infliximab

Worsening on Switching to Adalimumab



On Infliximab

On Adulimumab

Lupus Pernio Before and After two weeks after first dose of Infliximab

Baughman and Lower . Sarcoidosis 2001; 18: 70-74.

Lupus Pernio after 4th dose Infliximab

Arm and Back Involvement from Sarcoidosis

Infliximab Treatment

After 4 mo

After 8 mo

CHEST Original Research

SARCOIDOSIS

The Treatment of Lupus Pernio*

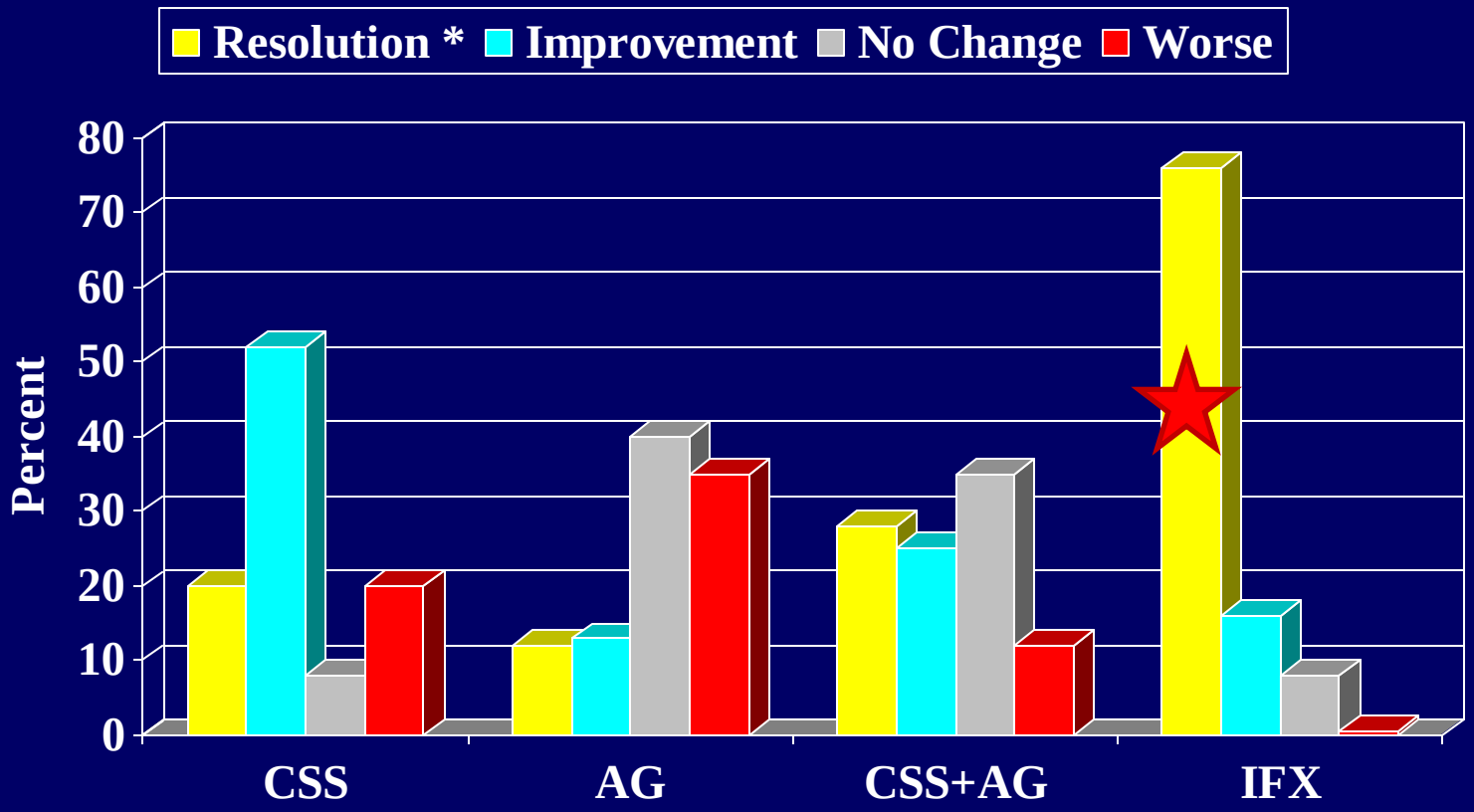
Results of 116 Treatment Courses in 54 Patients

Eleni Stagaki, MD; William K. Mountford, PhD; Daniel T. Lackland, DrPH; and Marc A. Judson, MD, FCCP

Treatment	N of treatments
CSS: corticosteroids alone	35
AG: drugs other than prednisone or infliximab	19
CSS+ AG: combined therapy	49
IFX: Infliximab	13
Total	116

Stagaki E, et al. Chest 2009; 135:468-476

Treatment of *lupus pernio*



Conclusions: Infliximab appears superior to systemic corticosteroids with or without additional agents for the treatment of lupus pernio. Noninfliximab, noncorticosteroid-containing regimens are of limited use for this condition. *(CHEST 2009; 135:468–476)*

Stagaki E, et al. Chest 2009; 135:468-476

Apremilast for Chronic Cutaneous Sarcoidosis

- **Apremilast** is a novel oral **immunomodulatory** agent that affects pro and anti-inflammatory mediators, including **TNF**, through targeted inhibition of phosphodiesterase type IV **(PDE4)**.
- Approved by the FDA in March 2014 for treatment of **active psoriatic arthritis**.
- It is also being tested for its efficacy in treating other chronic inflammatory diseases such as **AS, Behcet's disease, and RA**.

Baughman RP et al. Arch Dermatol 2012; 148:262-264

Aprelimast for Cutaneous Sarcoidosis Before and After 12 weeks therapy

Week 0

Week 12

Rituximab for Sarcoidosis

- T-reg cells may play a role in chronic sarcoidosis
- T-reg cells are affected by Rituximab
  - Prasse, A.et al. *Am J Respir Crit Care Med.* 2010 182:540-548
- Rituximab has a different toxicity profile than the anti-TNF regimens
  - Less cardiotoxic
  - No carcinogenicity

*** Rituximab may be considered as third-line therapy for refractory pulmonary sarcoidosis

THALIDOMIDE

- Drug with significant anti-inflammatory activity
- Inhibits TNF release by macrophages
- Treatment of *M. tuberculosis* patients with thalidomide reduces TNF release and is associated with weight gain
  - Tramontana et al Mol Med 1995; 1: 384-97.
- Has significant toxicity
  - *Teratogenic*
  - *Peripheral neuropathy*
  - *Somnolence*

Lupus pernio Before and After Four Months of Thalidomide

Before

After

Facial sarcoid before and after thalidomide

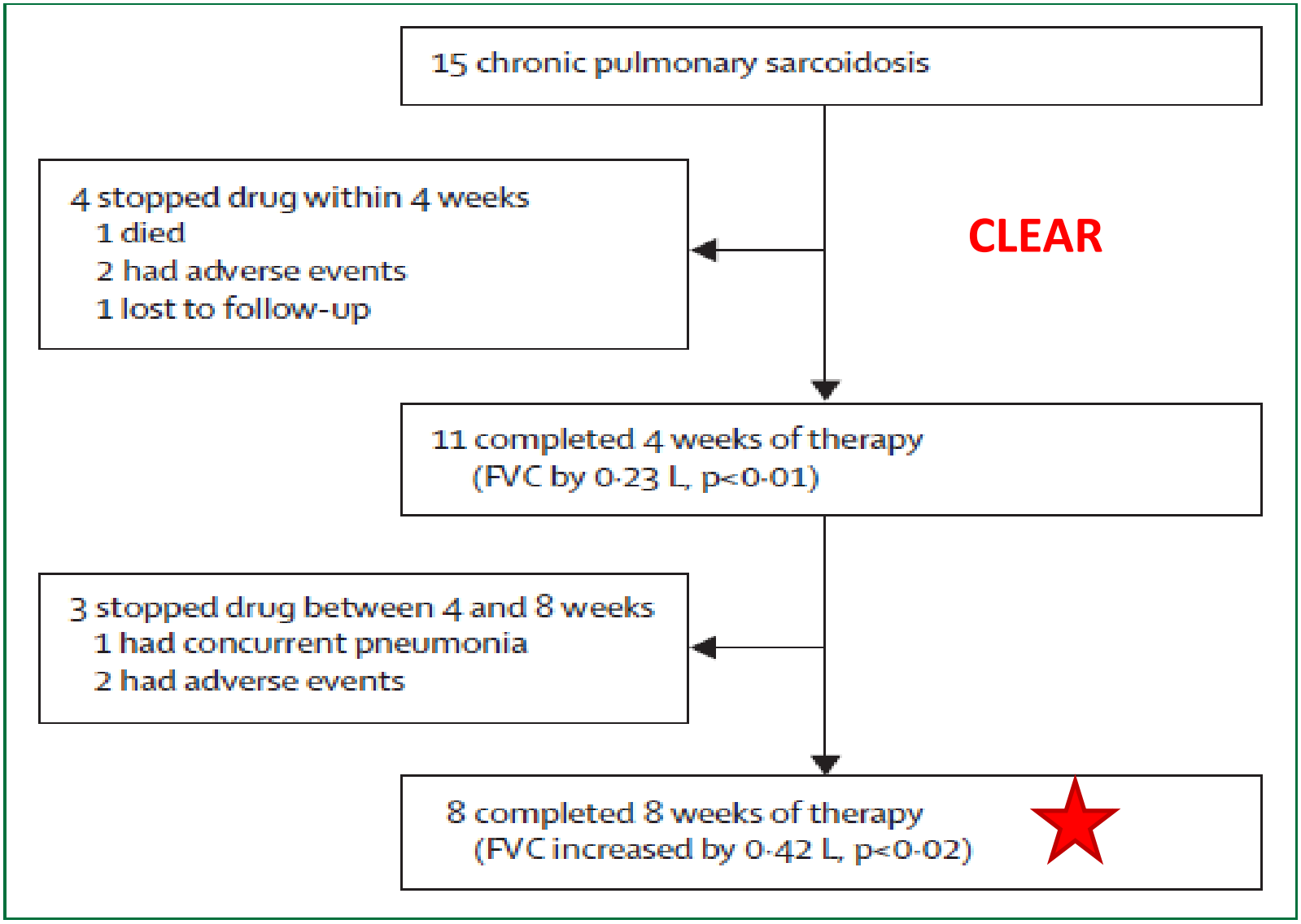


Figure 3: **Clinical outcome of 15 patients with sarcoidosis in an open-label, prospective trial of concurrent levofloxacin, ethambutol, azithromycin, and rifampin[55]**

FVC=forced vital capacity.

REFRACTORY SARCOIDOSIS

Failure/Toxicity Cytotoxic Drugs

Infliximab -Level 1A

Adalimumab -Level 2B

Consider other treatments

Rituximab -Level 1C

Thalidomide -Level 2C

Novel therapies

Aprelimast Level 1C

TREATMENT OF PULMONARY SARCOIDOSIS

Am J Respir Crit Care Med Vol 183. pp 573–581, 2011

- Chest X-ray stage 0/1
  - No symptoms
    - No systemic therapy
      - Level 1A (123)
- Chest X-ray stage 2 to 4
  - Symptomatic
    - Treat with corticosteroids
      - Level 1A (89, 123)
    - Initial dosage of 20–40 mg prednisone or its equivalent
      - Level 1B (89, 124)
    - Treat for 12–24 mo
      - Level 1C (90, 91, 125)
- Steroid-sparing alternatives for chronic pulmonary sarcoidosis
  - Methotrexate
    - Dose of 5–15 mg once a week
      - Level 1A (126–128)
    - Folic acid 1 mg/d may reduce toxicity
      - Level 1B (129)
  - Azathioprine 50–200 mg daily
    - Level 1B (130, 131)
  - Leflunomide 10–20 mg daily
    - Level 1B (132)
  - Mycophenolate
    - Level 1C (101, 133, 134)
- Treatment of refractory sarcoidosis
  - Infliximab intravenously 3–5 mg/kg initially, 2 wk later, then once a month
    - Level 1A (18, 98)

New treatment strategies for pulmonary sarcoidosis: antimetabolites, biological drugs, and other treatment approaches

www.thelancet.com/respiratory Published online July 21, 2015

Robert P Baughman, Jan C Grutters

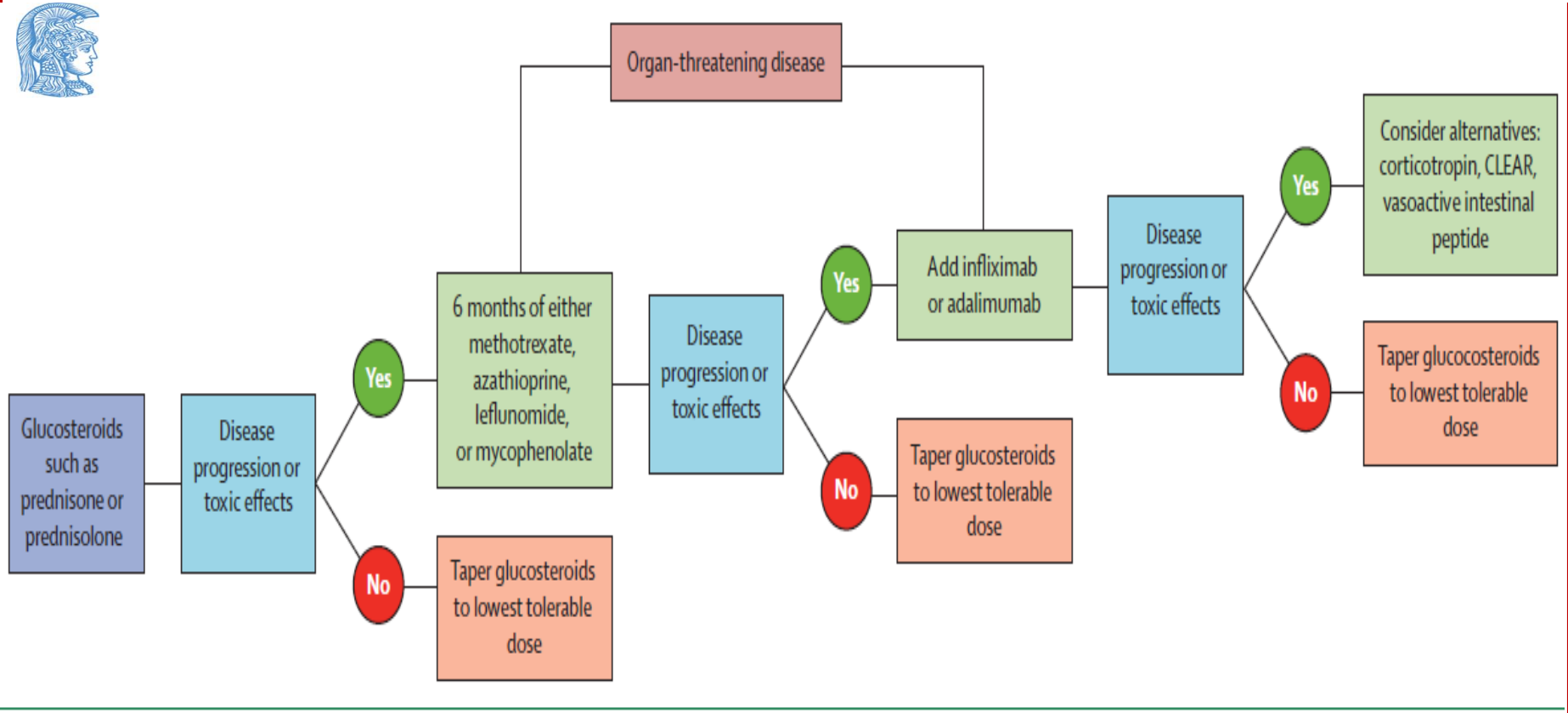


Figure 1: Decision tree for treatment of symptomatic sarcoidosis

Initial therapy is prednisone or prednisolone. The alternative to anti-tumour necrosis factor therapy includes CLEAR; rituximab; corticotropin; mesenchymal stem cells; and vasoactive peptides. CLEAR=concurrent levofloxacin, ethambutol, azithromycin, and rifabutin.

www.thelancet.com/respiratory Published online July 21, 2015

Key messages

- The treatment of sarcoidosis is usually a step-wise approach.
- Although glucocorticoids are the most widely used initial therapy for symptomatic pulmonary disease, steroid sparing drugs are useful in at least half of patients.
- Of the four antimetabolites that have been proved steroid sparing in chronic sarcoidosis, methotrexate is the most widely used on the basis of published clinical studies and toxic effects.
- The monoclonal anti-tumor necrosis factor antibody infliximab is effective in refractory sarcoidosis.
- New treatments for sarcoidosis such as multiantibitoic regimens and mesenchymal stem cells need to be studied.

VIEWPOINT

The Connection Between Evidence-Based Medicine and Shared Decision Making

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Evidence-based medicine (EBM) and shared decision making (SDM) are both essential to quality health care, yet the interdependence between these 2 approaches is not generally appreciated. Evidence-based medicine should begin and end with the patient: after finding and appraising the evidence and integrating its inferences with their expertise, clinicians attempt a decision that reflects their patient's values and circumstances. Incorporating patient values, preferences, and circumstances is probably the most difficult and poorly mapped step—yet it receives the least attention.[1] This has led to a common criticism that EBM ignores patients' values and preferences—explicitly not its intention.[2]

Shared decision making is the process of clinician and patient jointly participating in a health decision after discussing the options, the benefits and harms, and considering the patient's values, preferences, and circumstances. It is the intersection of patient-centered communication skills and EBM, in the pinnacle of good patient care (**Figure**).

One Without the Other?

These approaches, for the most part, have evolved in parallel, yet neither can achieve its aim without the other. Without SDM, authentic EBM cannot occur.[3] It is a mechanism by which evidence can be explicitly brought into the consultation and discussed with the patient. Even if clinicians attempt to incorporate patient preferences into decisions, they sometimes erroneously guess them. However, it is through evidence-informed deliberations that patients construct informed preferences. For patients who have to implement the decision and live with the consequences, it may be more pertinent to realize that it is through this process that patients incorporate the evidence and expertise of the clinician, along with their values and preferences, into their decision-making. Without SDM, EBM can turn into evidence tyranny. Without SDM, evidence may poorly translate into practice and improved outcomes.

> Without shared decision making, EBM can turn into evidence tyranny.

Likewise, without attention to the principles of EBM, SDM becomes limited because a number of its steps are inextricably linked to the evidence. For example, discussions with patients about the natural history of the condition, the possible options, the benefits and harms of each, and a quantification of these must be informed by the best available research evidence. If SDM does not incorporate this body of evidence, the preferences that patients express may not be based on reliable estimates of the risks and benefits of the options, and the resulting decisions not truly informed.

Why Is There a Disconnect?

A contributor to the existing disconnect between EBM and SDM may be that leaders, researchers, and teachers of EBM, and those of SDM, originated from, and historically tended to practice, research, publish, and collaborate, in different clusters. Some forms of SDM have emerged from patient communication, with much of its research presented in conferences and journals in this field. A seminal paper in 1997[4] conceptualized SDM as a model of treatment decision making and as a patient-clinician communication skill. However, it did so without any connection to EBM—perhaps not surprisingly, because EBM was in its infancy.[2]

Conversely, with its origins in clinical epidemiology, much of the focus of EBM has been on methods and resources to facilitate locating, appraising, and synthesizing evidence. There has been much less focus on discussing this evidence with patients and engaging with them in its use (sometimes even disparagingly referred to as "soft" skills). Most of the EBM attention has involved scandals (eg, unpublished data, results "spin," conflicts of interest) and the high technology milestones (eg, systems to make EBM better and easier). Information about using evidence in decision-making with patients has been scant.

Disconnect between the 2 approaches is also evident in, and maintained by, the teaching provided to clinicians and students, again often reflecting the backgrounds of their teachers. Opportunities to attend EBM teaching abound with content largely focused on forming questions and finding and critically appraising evidence.[5] Learning how to apply and integrate the evidence is usually absent, or mentioned in passing without skill training.

Realizing the Connection Between EBM and SDM

A logical place to start is by incorporating SDM skill training into EBM training. This will help to address not only the aforementioned deficits in EBM training but also the lack of SDM training opportunities presently available. Additionally, it may facilitate the uptake of SDM and, more broadly, evidence translation. Recent calls for SDM to be routinely incorporated into medical education present an immediate opportunity to capitalize on closely aligning the approaches.

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SARCOIDOSIS REVIEW ARTICLES

Concise Clinical Review

A Concise Review of Pulmonary Sarcoidosis

Robert P. Baughman[1], Daniel A. Culver[2], and Marc A. Judson[3]

Am J Respir Crit Care Med Vol 183. pp 573–581, 2011

Therapy for sarcoidosis: evidence-based recommendations

Expert Rev. Clin. Immunol. 8(1), 95–103 (2012)

CHEST Recent Advances in Chest Medicine

Recent Advances in Sarcoidosis

Adam S. Morgenthau, MD, FCCP; and Michael C. Iannuzzi, MD, MBA, FCCP

CHEST 2011; 139(1):174–182

www.thelancet.com/respiratory Published online July 21, 2015

N ENGL J MED 357;21 WWW.NEJM.ORG NOVEMBER 22, 2007

Sarcoidosis

www.thelancet.com Vol 383 March 29, 2014

Dominique Valeyre, Antje Prasse, Hilario Nunes, Yurdagul Uzunhan, Pierre-Yves Brillet, Joachim Müller-Quernheim